An Introduction to ToxCast™

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ToxCast™ is a chemical prioritization research program to develop the ability to forecast toxicity using bioactivity profiling. The point is to use results in a variety of in vitro and rapid non-mammalian in vivo assays to explore effects at different toxicity targets. The design of the study (from receptor-specific assays through cellular assays to evaluations of toxicity in zebrafish) allows data analysis to proceed in both unsupervised and supervised modes. In unsupervised modes, assay results are used to explore and define common toxicity pathways. Supervised analyses are used to develop predictors of animal toxicity as determined from a database of the results of toxicity testing using guideline registration studies. In Phase I of ToxCast™, just over 300 chemicals, largely registered pesticide active ingredients, have been tested in over 400 assays. Phase II will evaluate predictors derived in Phase I by testing toxicity predictions in an additional set of chemicals. While the initial phases of ToxCast™ have focused on hazard identification and prioritization, many assays have been run at multiple concentration levels, so concentration-response analysis is feasible. Combined with work developing PBPK models described in Dr. Clewell's talk in this session, such analysis could foster the development of purely in vitro-based dose-response analysis, as envisioned in the National Academy's recent document "Toxicity Testing in the 21st Century". All data collected in Phase I are being made available to the public, and investigators are encouraged to explore this rich dataset with their own methodologies. *This work was reviewed by EPA and approved for publication but does not necessarily reflect official Agency policy.*